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Can modulation of gut microbiota affect anthropometric indices in patients with non-alcoholic fatty liver disease? An umbrella meta-analysis of randomized controlled trials

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Background and aim: Modulating the gut microbiota population by administration of probiotics, prebiotics, and synbiotics has shown to have a variety of health benefits in different populations, particularly those with metabolic disorders. Although the promising effects of these compounds have been observed in the management of patients with non-alcoholic fatty liver disease (NAFLD), the exact effects and the mechanisms of action are yet to be understood. In the present study, we aimed to evaluate how gut microbiota modulation affects anthropometric indices of NAFLD patients to achieve a comprehensive summary of current evidence-based knowledge.

Methods: Two researchers independently searched international databases, including PubMed, Scopus, and Web of Science, from inception to June 2023. Meta-analysis studies that evaluated the effects of probiotics, prebiotics, and synbiotics on patients with NAFLD were entered into our umbrella review. The data regarding anthropometric indices, including body mass index, weight, waist circumference (WC), and waist-to-hip ratio (WHR), were extracted by the investigators. The authors used random effect model for conducting the meta-analysis. Subgroup analysis and sensitivity analysis were also performed.

Results: A total number of 13 studies were finally included in our study. Based on the final results, BMI was significantly decreased in NAFLD patients by modulation of gut microbiota [effect size (ES): −0.18, 95% CI: −0.25, −0.11, $P < 0.001$]; however, no significant alteration was observed in weight and WC (ES: −1.72, 95% CI: −3.48, 0.03, $P = 0.055$, and ES: −0.24, 95% CI: −0.75, 0.26, $P = 0.353$, respectively). The results of subgroup analysis showed probiotics had the most substantial effect on decreasing BMI (ES: −0.77, 95% CI: −1.16, −0.38, $P < 0.001$) followed by prebiotics (ES: −0.51, 95% CI: −0.76, −0.27, $P < 0.001$) and synbiotics (ES: -0.12, 95% CI: −0.20, −0.04, $P = 0.001$).

Conclusion: In conclusion, the present umbrella meta-analysis showed that although modulation of gut microbiota by administration of probiotics, prebiotics, and synbiotics had promising effects on BMI, no significant change was observed in the WC and weight of the patients. No sufficient data were available for other anthropometric indices including waist-to-hip ratio and waist-to-height ratio and future meta-analyses should be done in this regard.

Keywords: anthropometric indices, body mass index, gut microbiota, meta-analysis, Non-alcoholic fatty liver, probiotics, umbrella

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is known as one of the major causes of chronic liver diseases worldwide. It has affected over 30% of the world's population, and its prevalence rises annually in parallel to obesity and diabetes mellitus[1–4]. NAFLD consists of a wide range of liver pathologies resulting from fat accumulation in greater than or equal to 5% of hepatocytes without secondary causes, such as excessive consumption of alcohol. It can begin with steatohepatitis, progress to non-alcoholic steatohepatitis (NASH), and advance to fibrosis, putting the patient at risk of cirrhosis and hepatocellular carcinoma (HCC)[5–7].

Although the definite mechanisms leading to NAFLD are still unclear, multiple factors such as insulin resistance, genetic factors, diet, mitochondrial dysfunction, and lipotoxic lipids are some responsible mechanisms for the induction and progression of the disease[8–10]. Metabolic syndrome components (hyperglycaemia, hypertension, abdominal obesity, dyslipidemia) are important risk factors for NAFLD and are also significantly prevalent in these populations, reflecting a bidirectional relationship between the two conditions[11–13]. Obesity is a known risk factor for NAFLD as these patients experience higher obesity indicators, including BMI, waist circumference (WC), waist-to-hip ratio (WHR), and weight[14–17].

Currently, the main standard treatment for NAFLD is sustained weight loss through a lifestyle change that includes physical activity and a healthy diet[18]. Weight loss achieved by lifestyle modification leads to a decline in liver fat and improves insulin sensitivity and glucose control[19,20]. Nevertheless, many patients struggle with maintaining a healthy weight and lifestyle, highlighting the need for new therapeutic strategies for NAFLD. Despite several studies on different drugs, there is still a lack of any specific FDA-approved pharmaceutical options for treating NAFLD[7,21,22].

The role of the gut microbiome in the pathogenesis of NAFLD has garnered a great deal of attention in recent years and shed light on new treatment strategies[23–25]. One of the proposed strategies for the treatment of NAFLD is the modulation of the gut microbiome by the administration of probiotics, prebiotics, and synbiotics[26,27]. Probiotics are defined as live microorganisms which can selectively enhance some gut-microbiome strains. Prebiotics consist of fibers that can enhance special species of gut microbiota. Synbiotics are the combination of probiotics and prebiotics[28]. Although more research is required to establish the efficacy of these compounds in preventing and treating NAFLD, many studies have demonstrated a link between microbial modulation and enhancement in patients' liver enzymes, lipid profile, steatosis, and other factors[29–35]. Moreover, several surveys have suggested the favorable effects of gut-microbiome targeted therapies in weight control and BMI of obese and overweight patients[36,37]. Albeit, the role of gut microbial modulation on anthropometric indices is still controversial. Some meta-analyses reported significant effects of microbial modulation on BMI and weight control, while others found no favorable impacts[38–40]. Hadi and colleagues, in a meta-analysis study, showed no significant effect of synbiotic components on BMI and WC in NAFLD subjects, while Gkiourtzis and colleagues reported significant effects of probiotics on anthropometric characteristics in paediatrics with NAFLD[41,42].

HIGHLIGHTS

- There is a close association between gut microbiota and metabolic diseases including non-alcoholic fatty liver disease.
- Increased anthropometric indices like BMI, waist circumference and weight are main risk factors for non-alcoholic fatty liver disease.
- Modulation of gut microbiota by administration of probiotics and synbiotics can significantly reduce BMI.

Considering the important role of anthropometric characteristics and weight control strategies in the management of individuals with NAFLD in clinical settings, and due to the inconsistent results of meta-analyses on the effects of gut-microbiome modulation in this regard, we aimed to conduct an umbrella review of meta-analyses to summarize the results of the effectiveness of gut-microbiome modulation on anthropometric parameters of patients with NAFLD based on current evidence-based knowledge.

Material and methods

Search strategy and study selection

The present study is an umbrella review of meta-analyses of randomized control trials. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A354) guideline was used for reporting and conducting the study (Table S1, Supplemental Digital Content 2, http://links.lww.com/MS9/A355)[43]. To increase the quality of the study, We adhered to the AMSTAR 2 checklist, Supplemental Digital Content 3, http://links.lww.com/MS9/A356 which is used for assessing systematic reviews and meta-analyses quality[44]. The study protocol is previously registered in PROSPERO (CRD42022346998). We searched international databases, including PubMed/Medline, Web of Science, and Scopus, from inception up to June 2023 with the following keywords: "Nonalcoholic Fatty Liver Disease," "Nonalcoholic Steatohepatitis," "Gut microbiome," "Gut microbiota," "Prebiotics," "Probiotics," "Synbiotics," "anthropometric indices," "body mass index," waist circumference," "weight," "waist to hip ratio," "systematic reviews," and "meta-analysis.". Two researchers (E.A.S. and M.H.K.) performed the search process independently and the disagreements were finalized by a third researcher (S.H.). The reference lists of included studies were also searched.

Inclusion and exclusion criteria

Meta-analysis studies that evaluated the randomized controlled trials (RCTs) regarding the effects of probiotics, prebiotics, and synbiotics on anthropometric indices of patients with NAFLD were eligible for our umbrella review. We excluded systematic reviews without meta-analysis, narrative reviews, network meta-analyses, letters to editors, and commentaries.

Quality assessment

AMSTAR checklist 2 was used to assess the quality of included studies[44]. This checklist includes 16 questions regarding the

quality of systematic reviews and meta-analyses. The final quality is reported as "High", "moderate", "Low", and critically low".

Data extraction

Two researchers (E.A.S. and M.H.K.) extracted data from the included studies. Any discrepancies were resolved by a third researcher (S.H.). First author name, year of publication, study sample size, effect size (ES), and 95% CI of anthropometric indices, the tool used for risk of bias assessment, searched databases, and date of the search were extracted from included studies.

Data synthesis and statistical analysis

The overall Effect size ES of the impact of gut microbial modulation on anthropometric indices was calculated based on ES and 95% CI of included studies. When a meta-analysis study assessed more than one intervention, we behaved each intervention as a separate study. We used comprehensive meta-analysis (CMA) version 3 to conduct the meta-analysis. Heterogeneity was calculated using I2 statistics and Cochrane's Q-test. I^2 greater than 50% and *P* value less than 0.1 were considered as the significance level. Sensitivity analysis was conducted to determine each study's effect on total ES. We used random effect model for our analysis. Visual inspection of the funnel plot and Egger's regression test was applied to assess the publication bias, and for any suspected asymmetry, trim and Fill analysis was conducted[45,46].

Results

In the initial search, a total number of 338 studies were identified in the databases, and 35 studies were duplicated and omitted. A total of 303 studies went for the title and abstract evaluation, and 243 were irrelevant and were excluded. A total of 60 studies went for a full-text assessment, and 47 were omitted. Finally, a total number of 13 studies were included in the analysis. Figure 1 shows the study selection process.

Studies characteristics

Among the 13 included studies, eight used probiotics as their intervention; one used prebiotics, one used synbiotics, two used

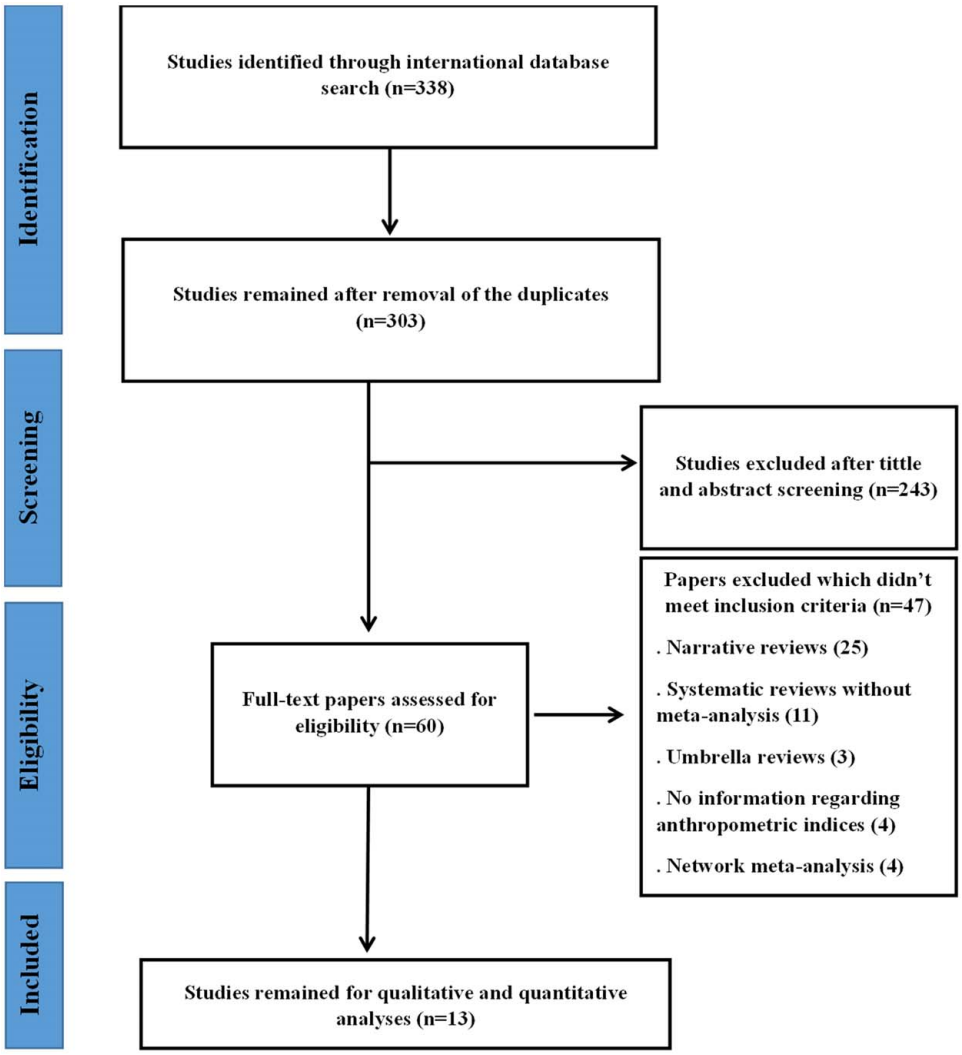

Figure 1. Study selection process.

Table 1

Characteristics of included studies

First author/year of publication	No. included studies	Total sample size	Data bases	Date of search	Intervention	Duration of treatment	Outcomes	Risk of bias assessment tool	Quality of included studies
Gkiourtzis *et al.*, 2022[41]	4	238	Medline/PubMed, Scopus and Embase	Up to September, 2021	Probiotics	8–16 weeks	BMI, WC	Cochrane	High quality
Hadi *et al.*, 2019[42]	11	419	PubMed, Scopus, ISI Web of science and Google Scholar	Up to December, 2017	Synbiotics	8–28 weeks	BMI, WC, weight	Jadad	Low quality
Huang *et al.*, 2022[47]	24	1403	Embase, PubMed, and Web of Science	Up to December, 2021	Probiotics	4–24 weeks	BMI	Cochrane and Newcastle-Ottawa Scale	Low quality
Koutnikova *et al.*, 2019[29]	12	660	Pubmed/Medline, EMBASE and the Cochrane Central/ 1990 to	Up to June, 2018	Probiotics	2–28 weeks	BMI, WC, weight	PEDro	High quality
Lavekar *et al.*, 2017[48]	7	296	PubMed, Cochrane, Embase,	Up to February, 2016	Probiotics	8–28 weeks	BMI	Jadad	Critically low quality
Liu *et al.*, 2019[39]	15	782	PubMed, Cochrane, and Embase/	Up to April, 2019	Probiotics and synbiotics	8–28 weeks	BMI, WC	Cochrane	Critically low quality
Loman *et al.*, 2018[40]	25	1309	PubMed and Embase/	Up to December, 2017	Probiotics, prebiotics, and synbiotics	8–24 weeks	BMI	Cochrane	Low quality
MA *et al.*, 2013[38]	4	134	Medline, Embase, Web of Science, Chinese Biomedicine Database and the China Journal Full Text	Not reported	Probiotics	8–24 weeks	BMI	Jadad	Critically low quality
Sharpton *et al.*, 2019[49]	21	1252	PubMed/Medline, Embase, and the Cochrane Library	Up to December, 2018	Probiotics and synbiotics	8–28 weeks	BMI	Cochrane	High quality
Stachowska *et al.*, 2020[32]	6	242	PubMed/MEDLINE, Embase, clinicaltrials.gov, Cinahl, Web of Science	Up to March, 2020	Prebiotics	10 and 12 weeks	BMI, weight	Cochrane	Low quality
Tang, 2019[50]	22	1356	PubMed, Embase, the Cochrane Library, the Web of Science; China National Knowledge Infrastructure (CNKI), Wan Fang Data, and VIP	Up to April, 2019	Probiotics	4–24 weeks	BMI, weight	Cochrane	High quality
Xiao,2019[51]	28	1555	PubMed, Embase, Cochrane Library, Web of Science, OVID, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, China Biology Medicine disc, and Wan fang Database	Up to April, 2019	Probiotics	4–28 weeks	BMI	Cochrane, Jadad	Critically low quality
Yang *et al.*, 2021[52]	9	352	PubMed, Cochrane, Medline, Web of Science and Embase	Up to April, 2021	Probiotics	8–48 weeks	BMI	Cochrane, Jadad	Critically low quality

WC, waist circumference.

both probiotics and synbiotics, and one used probiotics, prebiotics, and synbiotics. The total sample size of included studies was 9998, varying from 134 to 1555. BMI, WC, and weight were assessed in 13, 4, and 4 studies, respectively. Detailed information on all included studies is provided in Table 1. Among the included studies, four studies had high quality while four and five studies had low and critically low quality, respectively. Detailed information regarding the quality of included studies based on the AMSTAR 2 checklist is shown in Table S2, Supplemental Digital Content 4, http://links.lww.com/MS9/A357.

BMI

Based on the result of 17 effect sizes, gut microbial modulation could significantly reduce BMI in NAFLD patients (ES: – 0.18, 05% CI: – 0.25, – 0.11, $P < 0.001$) (Fig. 2). The results were heterogeneous ($I^2 = 71.84\%$, $P < 0.001$) and the sensitivity analysis results showed no significant change after removal of each study. The results of subgroup analysis showed probiotics had the strongest effect on decreasing BMI (ES: – 0.77, 95% CI: – 1.16, – 0.38, $P < 0.001$) followed by prebiotics (ES: – 0.51, 95% CI: – 0.76, – 0.27, $P < 0.001$) and synbiotics (ES: – 0.12, 95% CI: – 0.20, – 0.04, $P = 0.001$) (Fig. 2). Based on Egger's regression test result, significant publication bias was observed ($P < 0.001$). The trim and fill analysis result with seven imputed studies was compatible with our result (ES: – 0.25, 95% CI: – 0.44, – 0.05) (Fig. 3).

Weight

Based on the results of four effect sizes, the impact of gut microbial modulation on body weight in NAFLD patients was not significant (ES: – 1.72, 05% CI: – 3.48, 0.03, $P = 0.055$) (Fig. 4). The results were heterogeneous ($I^2 = 88.38\%$, $P < 0.001$). Sensitivity analysis showed that with the removal of Stachowska *et al.*[32] study, gut microbial modulation could significantly reduce weight in NAFLD patients (ES: – 2.69, 95% CI: – 3.40, – 1.99, $P < 0.001$). Due to the low number of included studies, we could not perform subgroup analysis and publication bias assessment.

Waist circumference

Based on the result of five effect sizes, the impact of gut microbial modulation on WC in NAFLD patients was insignificant (ES: – 0.24, 05% CI: – 0.75, 0.26, $P = 0.353$) (Fig. 5). The results were heterogeneous ($I^2 = 72.82\%$, $P = 0.005$). The results of sensitivity analysis showed the effect of gut microbial modulation on WC in patients with NAFLD changes after removal of Liu (Probiotics) and Liu (synbiotics) *et al.* (ES: – 0.92, 05% CI: – 1.96, 0.11, $P = 0.083$ ES: – 0.91, 05% CI: – 1.96, 0.12, $P = 0.085$, respectively)[39]. Based on the results of subgroup analysis, no significant effects on WC by probiotics (ES: – 0.93, 95% CI: – 2.18, 0.32, $P = 0.145$) and synbiotics (ES: – 0.10, 95% CI: – 0.66, 0.45, $P = 0.712$) were observed (Fig. 5). No study assessed the impact of prebiotics in this regard. Due to the low number of studies, we were not able to evaluate publication bias.

Discussion

To the best of our knowledge, the present study is the first meta-umbrella analysis assessing the effect of gut microbial modulation on anthropometric characteristics in patients with NAFLD. Obesity and overweight have a significant bidirectional relationship with NAFLD, and losing weight has revealed notable improvements in the liver's histology of such patients[53,54]. In NAFLD, reduction in mitochondrial oxidation of fatty acids, uptake of glucose, ketogenesis, and secretion of insulin occur along with increasing biosynthesis of triglyceride, lipogenesis, and cholesterol, which ultimately causes weight gain[55]. Even though NAFLD is a significant health problem, currently there is no approved medical therapy for this chronic condition, and management of the disease dramatically depends on changing

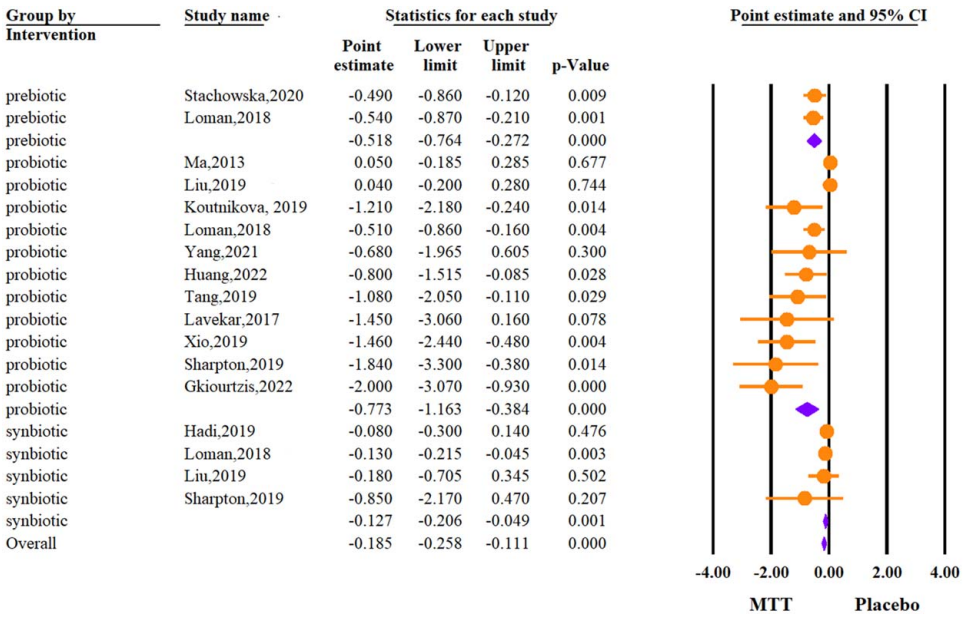

Figure 2. The effects of microbiome targeted therapy (MTT) on BMI of patients with. non-alcoholic fatty liver.

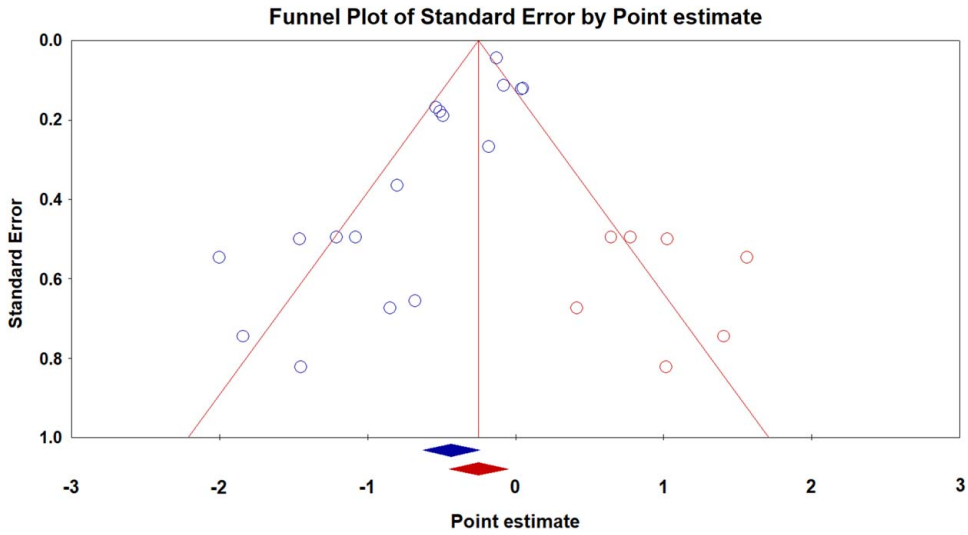

Figure 3. The results of publication bias with seven imputed studies (red dots).

dietary habits and increasing physical activity[53]. It is observed that obesity alters intestinal bacteria composition in rats and humans; hence, modifications of the intestinal bacterial content have been shown to affect obesity in NAFLD[56,57]. A vast body of literature has demonstrated the efficacy of gut microbial therapies in losing weight and enhancing lipid profiles in the management of obesity[58,59].

In the present study, we evaluated the effectiveness of gut microbial modulation as a treatment option by conducting an umbrella review on meta-analyses of RCTs on NAFLD subjects. In a total of 13 included meta-analyses, we found that administering prebiotics, probiotics, and synbiotics could significantly improve the BMI of patients with NAFLD. Although these compounds showed favorable effects on WC and weight, the pooled results were found to be insignificant. The insignificant impact of gut microbial modulation on WC and weight should be interpreted with caution since the number of included studies was relatively low and this finding may be changed by future studies. Moreover, the sensitivity analysis results suggest that upon the exclusion of Stachowska *et al.*[32], the impact of gut microbial modulation on weight becomes notably significant. Additional studies are warranted to thoroughly assess these findings.

Various studies have reported positive improvements in health-related outcomes following the consumption of probiotics, prebiotics, and synbiotics; for instance, preclinical research in cell models and animal trials showed potential probiotic benefits for the management of weight, hyperlipidemia, and insulin resistance[60–63].

Evidence showed that using multi-strain probiotics, including Lactobacillus, P. pentosaceus, and Bifidobacterium, probiotics in yogurts, including Streptococcus and Lactobacillus remarkably lowered BMI, weight, and WC in patients with NAFLD[64,65]. In addition, probiotics and synbiotics demonstrated promising outcomes in obese patients, particularly regarding BMI and fat mass. For example, VSL#3, a combination of eight probiotic strains, enhanced steatosis and BMI in obese children following four months of consumption[66,67]. It is reported that prebiotics could decrease plasma cholesterol and triglycerides and raise HDL levels in diabetes experiments[23]. In animal studies, oligofructose treatment decreased oxidative stress and adipose tissue inflammation and enhanced glucose tolerance and body weight, which was favorable in NAFLD patients[68]. Promising results were also observed with synbiotics regimens, including strains of Streptococcus plus fructooligosaccharides, Lactobacillus, Bifidobacterium, and inulin or guar gum with inulin[69–72].

Contrary to the aforementioned findings, Bomhof *et al.*[73] observed that a 36-week prebiotics administration of fructooligosaccharides did not change body composition. This scenario suggests that the efficacy of probiotics, synbiotics, and prebiotics

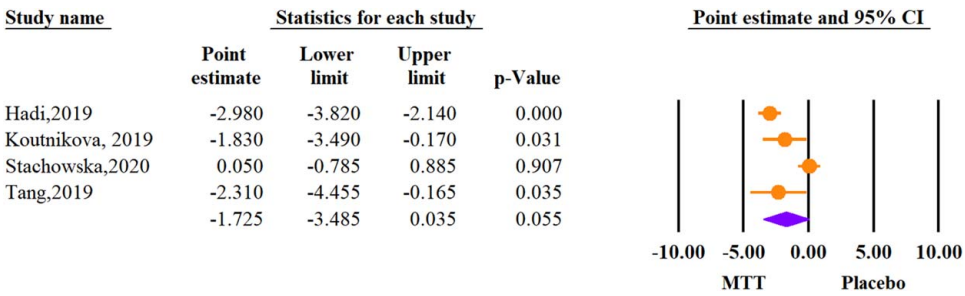

Figure 4. The effects of microbiome targeted therapy (MTT) on weight of patients with non-alcoholic fatty liver.

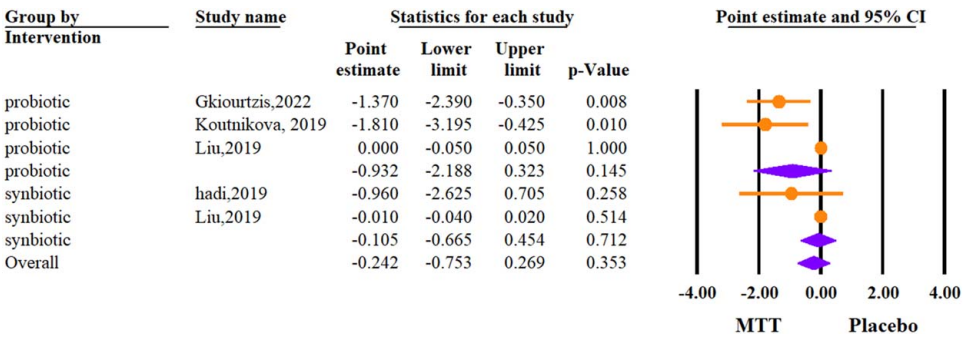

Figure 5. The effects of microbiome targeted therapy (MTT) on waist circumference of patients with non-alcoholic fatty liver.

on anthropometric factors is strongly associated with the microbial content of supplements[27].

The exact mechanisms of how gut microbial modulation can enhance anthropometric indices are very complex and need to be fully understood. Some postulated mechanisms are as follows: decreasing appetite, decreasing lipopolysaccharide (LPS) induced inflammation by enhancing the intestinal barrier and antimicrobial peptide production, reducing cholesterol absorption and synthesis, and increasing lipolysis and fatty acid oxidation. These mechanisms will be discussed in more detail.

Effects of gut microbial modulation on appetite

Probiotics affect appetite through the production of short-chain fatty acids (SCFAs), which results in increasing specific intestinal peptides, including peptide YY and glucagon-like peptide 1 (GLP-1)[74]. These hormones can lower appetite leading to lower calorie consumption and subsequent weight loss[75,76]. In addition, some SCFAs, like propionic acid and acetic acid, can stimulate adipose tissue to secret leptin and adiponectin, which have anorectic characteristics[77,78] (Fig. 6).

Gut microbial modulation and intestinal barrier

Probiotics help reduce intestinal permeability by enhancing the mucosal layer and tight-binding proteins between epithelial cells[79–82]. This may reduce the risk of low-grade inflammation in obesity, which results from elevated plasma LPS and proinflammatory cytokine levels released by special gut microbiota strains. This inflammatory state can cause insulin resistance, oxidative stress, and increased visceral fat deposition[83] (Fig. 6).

Effects of gut microbial therapies on antimicrobial peptides

Probiotics can stimulate the production of Cathelicidin and Defensins, two molecules with antimicrobial properties[84,85]. Production of such substrates prevents the proliferation of opportunistic pathogens and their products like indole and LPS in the gastrointestinal tract, which results in a less inflammatory state[64] (Fig. 6).

Impacts of gut microbial modulation on cholesterol absorption and production

The absorption of cholesterol, which is present in the intestinal medium, occurs through special receptors on enterocytes calling Niemann–Pick C1 like 1[65,86]. Previous studies have shown that probiotics can reduce the expression of these receptors leading to less cholesterol absorption. Less cholesterol absorption can cause weight loss[87,88]. SCFAs produced by probiotics like propionate and butyrate can inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is a key enzyme in cholesterol synthesis, thus reducing serum cholesterol levels[66,67] (Fig. 6).

Gut-microbiome therapies and adipose tissue and liver

Probiotics like Bifidobacterium and Lactobacillus produce conjugated linoleic, positively affecting energy metabolism and stimulating lipolysis[89]. Another mechanism that probiotics provide to reduce fat cell size is decreasing the absorption of fatty acids and enhancing the expression of genes related to fatty acid oxidation[90]. Probiotics can cause Adenosine monophosphate kinase phosphorylation, which reduces fat accumulation in the liver[91] (Fig. 6).

Strengths and limitations and future prospectives

Overall, in this study, we assessed the total effects of gut microbial modulation on anthropometric indices in the NAFLD population. Also, when possible, we conducted subgroup analysis to observe how probiotics, prebiotics, and synbiotics work separately. We also tried to illustrate some postulated mechanisms regarding the pathophysiological events of these compounds in their host body.

While the results of the current umbrella study suggest a promising effect of gut microbial modulation on BMI, several limitations in the clinical application of this approach persist, including variability in the host's microbiome population. Future studies should take into account the individual's specific microbiome when assessing the efficacy of gut modulation treatments. In addition, while there have been encouraging studies exploring the impact of altering the gut microbiome on NAFLD, the existing evidence is still constrained. Implementing interventions to modify the gut microbiome may necessitate intricate therapeutic strategies, including the use of particular probiotics and prebiotics, which may pose potential risks and require vigilant monitoring. It remains a fact that there is currently no conclusive agreement on specific therapies for gut-microbiome adjustment in the context of NAFLD. In essence, despite the promising potential of gut-microbiome modulation in treating NAFLD, significant limitations must be addressed before these approaches can be widely adopted in clinical practice.

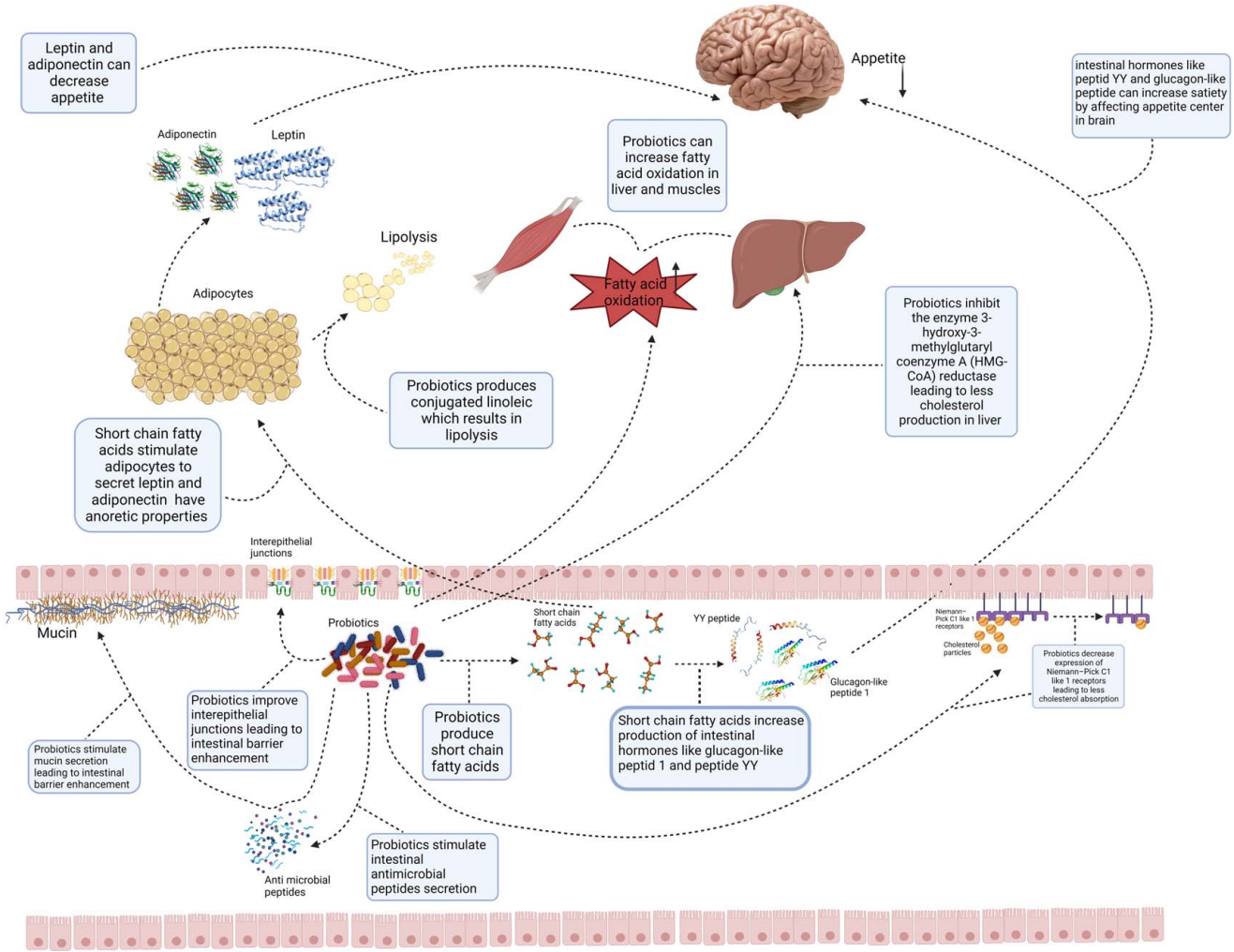

Figure 6. Mechanisms of the effects of gut microbial modulation in the enhancement of anthropometric indices.

Our study had some other limitations; first, the number of included meta-analyses was low for weight and WC. Second, no study assessed the effect of prebiotics on WC. In addition, included meta-analyses did not compare different probiotic bacterial strains to evaluate how different bacterial species work in the host. Moreover, most included meta-analyses did not perform trial sequential analysis or power analysis to assess the robustness of their results. We highly recommend such analyses for future studies. We also suggest future dose-response studies to estimate the optimum dose of these compounds.

Conclusion

In the present meta-umbrella study, we demonstrated the promising effect of gut microbial modulation by administration of probiotics, prebiotics, and synbiotics on the BMI of patients with NAFLD. However, the effects of these compounds were not significant on weight and WC. As lowering BMI is one of the treatment goals in NAFLD management, gut microbial modulation can be considered an adjuvant therapy along with lifestyle modification in NAFLD patients.

Ethical committee approval

This systematic review and meta-analysis do not require an ethical approval.

Consent

Since we did not have any human or animal subject, conducting this section is not applicable.

Source of funding

None.

Author contribution

Concept development (provided idea for the research): E.A.S., S. H. and A.V. Design (planned the methods to generate the results): E.A.S., and S.H. Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): S. H., S.S.N, F.M.G., and F.J. Data collection/processing

(responsible for experiments, patient management, organization, or reporting data): E.A.S., M.H.K., N.N, and A.B. Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): E.A.S, S.S.N, and M.H.K. Literature search (performed the literature search): M.S.A., G.M, and A.V. Writing (responsible for writing a substantive part of the manuscript): All authors.

Conflicts of interest disclosure

The authors declare that they have no conflict of interest.

Research registration unique identifying number (UIN)

The study protocol was registered in PROSPERO with the registration code CRD42022346998.

Guarantor

Soheil Hassanipour.

Data availability

The datasets used and/or analyzed during the current study are accessible from the corresponding author on reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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